A STUDY OF REACTIONS OF GRIGNARD REAGENTS AT LOW TEMPERATURES[1]

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The effect of temperature on the course and extent of reactions involving Grignard reagents has rarely been studied below $-30°$. The outstanding example of a successful result at extremely low temperatures is the formation of acids by treatment of Grignard reagents with solid carbon dioxide (1). Recently it has been shown that at about $-70°$ acetic anhydride reacts with various Grignard reagents to form the corresponding methyl ketones in high yield (2). In this paper we report on further studies of this reaction technique and demonstrate the reason for its success.

Effect of temperature. We have studied the reaction which takes place when a solution of butylmagnesium bromide is added to a solution of acetic anhydride in ether at different temperatures. It was found that from the reflux temperature of ether to about $-40°$ the yield of ketone remained almost constant at 50%.[2] However, the yield increased rather sharply on further cooling and reached 79% near $-70°$. One experiment indicated that by going to lower temperatures higher yields might be obtained. However, because of the inconvenience we did not explore this region further. This temperature effect seemed to be about the same in the reaction of *t*-butylmagnesium chloride with acetic anhydride and of phenylmagnesium bromide with benzoic anhydride. At $-70°$ each gave ketone in about 80% yield but at $0°$ the yields were about 50%. We did not investigate these cases further but assumed that they were approximately the same as for the case of *n*-butylmagnesium bromide and acetic anhydride. Our results are summarized in Table I.

The reactions were carried out in a special double-walled flask, shown in Figure 1. The *n*-butylmagnesium bromide was prepared and stored under pure dry nitrogen. The strength was determined by the acid titration method (4). Each run described in Table I involved the addition of 125 cc. of 2.03 *M* *n*-butylmagnesium bromide (0.257 mole) slowly over a period of two hours to a well-stirred solution of 55 g. (0.54 mole) of pure acetic anhydride in 125 cc. of dry ether. The temperature during the addition was recorded on a thermometer dipping into the liquid and was maintained at the desired point by a suitable cooling mixture or by the reflux of a suitable liquid in the outer jacket. After stirring for two hours after the addition was complete, the reaction mixture was allowed to come to $-10°$ and then treated with a saturated solution of ammonium chloride. The ether layer was separated and washed with 5% sodium hydroxide to remove acetic anhydride and acetic acid and then with saturated sodium chloride. Any ketone in the washings was

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[2] Fournier (3) treated a series of primary halide Grignard reagents with a series of anhydrides at about $-20°$ and reported yields in the range of 25-50%.

recovered by further ether extraction and added to the main batch. After filtration through anhydrous sodium sulfate the ether solution was treated in two ways to determine the amount of butyl methyl ketone: (a) titration of two 15-cc. aliquots (5); (b) isolation by careful fractionation of the remainder through a small packed column of about two plate

TABLE I

EFFECT OF TEMPERATURE ON YIELD OF 2-HEXANONE

REACTION TEMPERATURE °C	YIELD, % KETONE	METHOD OF ANALYSIS[a]	NUMBER OF EXPT'S
−82	83	t	1
−67	79	t, f	5
−54	64	t	2
−46	68	t	4
−37	51	t, f	3
−26	50	f	1
+ 5	48	t, f	2
+34[b]	48	t, f	3

[a] "t" indicates that the amount of ketone was determined by the titration method; "f" means the ketone was isolated by fractionation through a 6-inch column. The amount of ketone was considered to be the fraction boiling over a two-degree range around 126°, plus half of the material boiling in the region 100–125°. This usually amounted to an additional 5%.
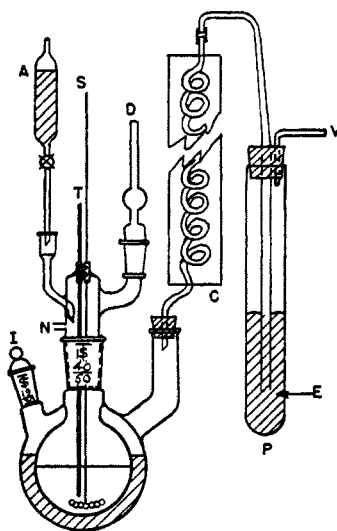
[b] No cooling bath was used.

FIG. 1. DOUBLE WALLED FLASK

efficiency. After a number of runs showed that the values obtained by isolation ran uniformly 3 to 5% lower than the titration values, only the titration method was used. The butyl methyl ketone was characterized by its boiling point, 125–127°, and by the formation of its semicarbazone, m.p. and mixed m.p. 121–122° (6).

Effect of variations from standard technique. Our studies show that the use

of excess acetic anhydride does little to improve the yield and that a good commercial grade is about as satisfactory as redistilled anhydride. The concentration of the ethereal anhydride solution is relatively unimportant. The rates at which the Grignard reagent is added should not exceed one-third of a mole per hour for best results, but even with very rapid addition the yield of ketone is quite high. Precooling of the Grignard reagent is generally unnecessary. Rapid stirring during the addition period is important. Reversal of the order of addition, *e.g.*, adding anhydride to Grignard reagent, causes a large drop in yield. The results are summarized in Table II.

Effect of variation of Grignard reagent and anhydride. The preparation of ketones by this method seems to be quite general. Primary, secondary, tertiary, and aromatic Grignard reagents gave high yields when reacted with acetic,

TABLE II

EFFECT OF VARIATION FROM STANDARD TECHNIQUE ON YIELD OF KETONE

CONDITIONS[a]	YIELD IN %[b]
Standard (for Table I)	79
Equal molar amount of anhydride	74
Equal molar amount of anhydride T = 30–34°	39
Rapid addition, 0.3 moles in 50 minutes	75
Rapid addition, 0.1 moles in 2 minutes[c]	61
Commercial anhydride[d]	77
Less ether (25 cc. of ether to 55 g. of anhydride)	80
No nitrogen atmosphere	67*
Anhydride added to Grignard reagent	39*

[a] All conditions except those noted in this column were the same as those described as standard for Table I.

[b] Yields are based on from two to five experiments except those yields marked with an asterisk (*) which were single runs.

[c] The temperature rose to −60° during this addition.

[d] Carbide and Carbon product.

propionic, and butyric anhydrides. With chloroacetic anhydride the yield fell to 35–50%, but this method appears at least comparable to other methods of preparing chloromethyl ketones using organometallic reagents (7, 8). It was rather surprising that good yields of keto acids could be obtained by using a cyclic anhydride in spite of the low solubility of these substances at low temperature. We did not investigate this phase to any great extent but did secure encouraging results. It would appear that this procedure will prove very useful in the preparation of certain β-aroylpropionic acids not directly obtainable by the Friedel-Crafts method. Our results are summarized in Table III.

Low temperature reactions with other compounds. We investigated the reaction of Grignard reagents with esters and acid chlorides but found little improvement over the corresponding reactions when carried out at room temperature. In these cases it is noteworthy that no insoluble complex separates during the reaction. This is significant for we believe that the nature of the insoluble complex

formed in the anhydride reaction accounts for the success of the low temperature technique.   The arguments for this view are presented below.

We found that diisopropyl ketone and n-propylmagnesium bromide react at $-70°$ to give addition and reduction products in the same ratio as found pre-

TABLE III

VARIATIONS IN ANHYDRIDE AND GRIGNARD REAGENT

$(RCO)_2O + R'MgX \rightarrow RCOR' + RCO_2MgX$

R	R'	YIELD, % KETONE[a]
CH₃	CH₃CH₂CHCH₃	80[b], 75[c]
CH₃	(CH₃)₃C	78[b], 74[c]
CH₃	C₆H₅	75[b], 73[c]
CH₃CH₂	CH₃CH₂CH₂CH₂	74[b]
CH₃CH₂CH₂	CH₃CH₂CH₂CH₂	73[b]
C₆H₅	C₆H₅	87[b], 75[d]
ClCH₂	CH₃CH₂CH₂CH₂	35 to 50[c,e]
Succinic anhyd.	C₆H₅	50–70[f]
Succinic anhyd.	o-CH₃C₆H₄	35[g]

[a] Based on the Grignard reagent.

[b] As determined by titration method, Bryant and Smith, J. Am. Chem. Soc., **57**, 57 (1935).

[c] Our methyl isobutyl ketone boiled at 116–119° (Heilbron "Dictionary of Organic Compounds", Oxford University Press, New York, N. Y., 1943, Vol. II, pg. 639 gives 118°). Our pinacolone boiled at 104–106° (Heilbron, Vol. III pg. 493 gives 103–106°).   Our acetophenone, b.p. 198–202°, (Heilbron, Vol. I, pg. 15 gives 202°).

[d] Isolated as the oxime m.p. 141–143° (Heilbron, Vol. I. pg. 226, m.p. 144°).   The solvent used for the anhydride in this reaction consisted of equal weights of ether and toluene.

[e] The yield is particularly sensitive to experimental conditions.   In these reactions the ethereal reaction mixture was washed with 5% sodium carbonate solution instead of sodium hydroxide.   The product was isolated as a pink lachrymatory liquid, n_D^{25} 1.4400, b.p. 70–71° at 15 mm., which darkened on standing.   Verbanc and Hennion, J. Am. Chem. Soc., **60**, 1711 (1938) give b.p. 73–74° at 20 mm., n_D^{24} 1.4370.

[f] The solvent for the anhydride was 80% ether and 20% pyridine (by weight).   The Grignard reagent was added very slowly.   The yield of crude acid, m.p. 95–110° was 70%. Recrystallization from water gave the product m.p. 115–116°, neutral equivalent 181 (theory 178) in 50% yield.

[g] The solvent for the anhydride was 60% pyridine, 40% ether, by weight.   The reaction became very pasty; it was worked up by neutralizing with sodium carbonate after hydrolysis, and steam distilling the solvents.   The crude acid obtained on acidification melted from 88 to 100°.   Crystallization from water gave 35.2% of the theoretical amount of keto acid, m.p. 98–102°, neutral equivalent 190 (molecular weight 192).   Analysis, calculated as $C_{11}H_{12}O_3$.   Carbon, calculated 68.7%, found 68.7.   Hydrogen, calculated 6.3%, found 6.4.

viously (9).   In the case of 1:2 and 1:4 addition to α,β-unsaturated ketones, we found the same ratio in the case of ethylmagnesium bromide and benzalacetophenone at $-70°$ as Kohler formed in the range -37 to $35°$ (10).

Of particular interest are our findings with regard to m-nitrobenzaldehyde. Ordinarily it is considered unwise to attempt to react Grignard reagents with

functional groups in compounds containing a nitro group because of the ready reaction of this group. We were able to isolate phenyl *m*-nitrophenyl carbinol in 77% yield (based on Grignard reagent) from the reaction at −70° of phenylmagnesium bromide with *m*-nitrobenzaldehyde. However, with butylmagnesium bromide only tarry products were obtained.

Grignard reactions with di-isopropyl ketone. A solution of 50 g. (0.44 mole) of di-isopropyl ketone in 50 cc. of ether was added dropwise over a period of two hours to 0.625 mole of *n*-propylmagnesium bromide in 500 cc. of ether at −70°. After 5 hours at −70°, the mixture was allowed to come to room temperature and stand for 10 hours. After hydrolysis with dilute sulfuric acid the product was distilled to yield two fractions: 34.5 g., b.p. 120–140°; and 16.2 g. (23%), b.p. near 100° at 50 mm. The higher-boiling fraction was taken as *n*-propyl di-isopropyl carbinol. By the usual ketone titration (5) the lower-boiling fraction was shown to contain 17 g. of ketone (calculated as starting ketone). Assuming the remainder to be di-isopropyl carbinol, the yield of reduction product was 34%. A similar reaction except that the temperature of reaction was 30° gave 18.5% of tertiary alcohol, 23% of unreacted ketone, and 39% of reduction product (9).

Grignard reactions with benzalacetone. In the usual apparatus 30 g. (0.205 mole) of benzalacetone in ether was added dropwise to 0.292 mole of ethylmagnesium bromide at −70°. After 12 hours an excess of alcohol was added and the reaction mixture hydrolyzed at room temperature with ammonium chloride. On distillation there was obtained 31 g. (81%) of a fraction b.p. 138–145° at 25 mm. On treatment in acetone with potassium permanganate the unsaturated alcohol was destroyed (10). The remaining saturated ketone amounted to 17.5 g. (57% of the reaction products), b.p. 136° at 22 mm. In a similar reaction except that the Grignard reagent was added to the benzalacetone, the yield of mixed 1:2 and 1:4 addition products was less than 40% but the ratio was about the same. When this reaction was repeated at 30°, the same products in the same ratio were obtained.

Grignard reactions with m-nitrobenzaldehyde. An ether solution containing 0.196 mole of phenylmagnesium bromide (by titration) was added over a period of two hours to a solution of 47 g. (0.312 mole) of *m*-nitrobenzaldehyde in 650 cc. of toluene at −70°. After stirring for two hours more, an excess of alcohol was added (to decompose unreacted Grignard reagent) and the reaction mixture was treated with dilute hydrochloric acid. The carbinol distilled at 208–212°/6 mm. as a thick oil which crystallized, on long standing at 0°, and melted at 68–71°. A similar experiment at room temperature yielded only intractable tar.

Anal. Calc'd for $C_{13}H_{11}NO_3$: C, 68.1; H, 4.8; N, 6.1.

Found (on liquid): C, 68.3, 68.2; H, 5.0, 4.8; N, 6.2, 6.3.

The 3,5-dinitrobenzoate was prepared, and melted at 119.5–121.0° on crystallization from alcohol.

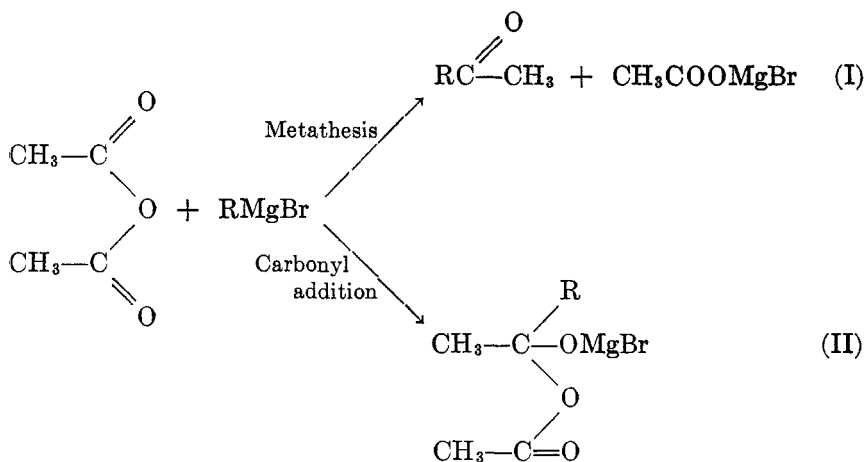Anal. Calc'd for $C_{20}H_{13}N_3O_8$: C, 56.8; H, 3.2; N, 9.9.

Found: C, 56.9, 56.8; H, 3.2, 3.6; N, 9.6, 9.5.

On oxidation at 60° with sodium dichromate (3 g.) and sulfuric acid in water the carbinol (2.5 g.) was converted into 1.5 g. of *m*-nitrobenzophenone (11) m.p. 93-95°.

Mechanism of the reaction between Grignard reagents and anhydrides. The mechanism of the reaction of Grignard reagents with acid anhydrides has not received much attention. Mechanisms for reactions between Grignard reagents and several acid derivatives have been discussed (12).

Two main courses are in general possible: The Grignard reagent may add to the carbonyl groups; or it may enter into a metathetical type reaction with some other linkage of the acid derivative (such as the chlorine in an acid chloride).

We have convincing evidence that with acetic anhydride at $-70°$ the reaction follows the second path as shown below.

$$
\begin{array}{c}
\text{CH}_3\text{—C}\overset{\displaystyle O}{\diagdown} \\
\qquad \text{O} \ + \ \text{RMgBr} \\
\text{CH}_3\text{—C}\underset{\displaystyle O}{\diagup}
\end{array}
\quad
\begin{array}{l}
\xrightarrow{\text{Metathesis}} \quad \text{RC}\overset{\displaystyle O}{\diagup}\text{—CH}_3 \ + \ \text{CH}_3\text{COOMgBr} \quad \text{(I)} \\[2em]
\xrightarrow[\text{addition}]{\text{Carbonyl}} \quad
\begin{array}{c}
\text{R} \\
\text{CH}_3\text{—C—OMgBr} \\
\text{O} \\
\text{CH}_3\text{—C=O}
\end{array}
\quad \text{(II)}
\end{array}
$$

It was observed that when a solution of butylmagnesium bromide was added to a solution of acetic anhydride in ether at $-70°$ a white precipitate began to form immediately and increased in amount all during the addition. This precipitate might have been (a) the bromomagnesium acetate formed in accordance with equation (I); (b) the addition product (R = butyl) shown in equation (II); (c) a complex formed between anhydride and Grignard reagent, such as $(\text{CH}_3\text{CO})_2\text{O}\cdot\text{C}_4\text{H}_9\text{MgBr}$; or (d) a complex formed between 2-hexanone and bromomagnesium acetate, $\text{C}_4\text{H}_9\text{COCH}_3\cdot\text{CH}_3\text{COOMgBr}$. We found that the clear supernatant solution (which could be separated from the insoluble compound) contained only traces of ketone, either before or after treatment with dilute acid. This experiment rules out (a). When the insoluble complex was treated at $-70°$ with an excess of alcohol, and the reaction mixture then treated with dilute acid, the ketone was formed in the usual high yield. This experiment rules out a complex such as (c) since such a complex would be decomposed by alcohol to yield butane and not ketone. In another experiment, the reaction mixture was allowed to come to room temperature from $-70°$. An insoluble complex was still present (undoubtedly $\text{CH}_3\text{COOMgBr}$) but now the entire amount of ketone was shown to be in the ether solution. Furthermore, if the solution at room temperature was cooled back to $-70°$, the entire amount of ketone still remained in the ether layer. These experiments prove that the original insoluble complex (at $-70°$) is thermally unstable and on cooling does not form again. If the original complex (at $-70°$) were (d) then on cooling the mixture from room temperature to $-70°$, the original complex should be regenerated and the ketone would not be in solution. The above facts are consistent with the hypothesis that the reaction follows the course indicated by equation (II). The insolubility and thermal stability of this complex at the low

temperatures involved are probably the reasons for the success of the low temperature technique.

We have made another observation which is quite interesting and may on occasion be of considerable importance in running competitive Grignard reactions. When an ethereal solution of 2-hexanone was stirred at $-65°$ with excess of n-butylmagnesium bromide for thirty minutes, only about 20% had reacted whereas under similar conditions acetic anhydride reacted almost completely. Such a result is surprising in view of the relative reactivity of acid derivatives and ketones at ordinary temperatures (13).

SUMMARY

A study of the reaction of Grignard reagents with various compounds at low temperature is described. With anhydrides ketones are obtained in excellent yield, and the effect of temperature of reaction on yield of ketone is described in detail for the reaction of n-butylmagnesium bromide with acetic anhydride.

It is shown that n-butylmagnesium bromide adds to a carbonyl group of acetic anhydride at $-70°$. The stability and insolubility of this addition product account for the high yield of ketone obtained.

It is possible to react phenylmagnesium bromide, but not butylmagnesium bromide, with m-nitrobenzaldehyde at $-70°$ but not at $0°$ to obtain m-nitrobenzohydrol in high yield.

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